("Final Office Action"). A copy of pending claims 15 and 24-29 are presented in APPENDIX I.

II. Rejection of the Claims Under 35 U.S.C. § 103(a)

In the Final Office Action, the Examiner maintained the rejection of claims 15 and 24-28 under 35 U.S.C. § 103(a) as being unpatentable over Emilie *et al.* (Blood, 1994, Vol. 84, pp. 2472-2479) in view of Sato *et al.* (Cancer Research, 1993, Vol. 53, pp. 851-856).

The Examiner concluded that these two prior art references rendered certain elements of the claimed invention inherently obvious based on teachings in Applicants' own specification. Applicants submit that the Examiner provided no evidence that one of skill in the art at the time of filing would have recognized that every element of the claimed invention was necessarily present in the prior art. Neither Emilie *et al.* nor Sato *et al.*, either alone or in combination, taught or suggested all elements of the claimed invention. Thus, the Examiner has not established a *prima facie* showing of obviousness under 35 U.S.C. § 103(a). Applicants respectfully request reconsideration of the present application for the reasons discussed below.

M.P.E.P. 2141.02: Disclosed Inherent Properties are Part of "As a Whole" Inquiry

Regarding claims 15 and 25-28, the Examiner asserted that at least one recited element in the claims (e.g., "to suppress elevation of blood levels of ionized calcium") was rendered obvious by the teachings of Emilie *et al.* and Sato *et al.*, despite the fact that neither reference suggested a method of using an anti-IL-6R antibody to reduce blood levels of ionized calcium in cachexia patients. The Examiner based this contention on M.P.E.P. 2141.02, reciting the passage that states: "In delineating the invention as a whole, we look not only to the subject matter which is literally recited in the claim in question . . . but also to those

properties of the subject matter which are *inherent in the subject matter and are disclosed in the specification* . . . ." (Emphasis in Final Office Action).

Based on this passage, the Examiner suggested that it was appropriate to find a recited element inherently obvious based on a teaching in Applicants' specification, regardless of what the prior art teaches. To the contrary, M.P.E.P. 2141.02 explains that: (1) the Examiner must consider the invention "as a whole"; and (2) the invention as a whole includes not only the subject matter literally recited in claims, but also the "properties of the subject matter which are inherent in the subject matter and are disclosed in the specification." In other words, the passage explains what is meant by the invention "as a whole," which is what the Examiner must consider when determining whether the claims are obvious in light of the prior art. M.P.E.P. 2141.02 does not suggest, however, that a claim may be rendered obvious by teachings in the specification disclosing a recited (or inherent) claimed feature when that feature is not taught or suggested anywhere in the prior art.

In fact, M.P.E.P. 2141.02 further explains that "[o]bviousness cannot be predicated on what is not known at the time an invention is made, even if the inherency of a certain feature is later established. *In re Rijckaert*, 9 F.2d 1531, 28 USPQ2d 1955." Moreover, an Examiner must provide evidence that "the missing descriptive matter is necessarily present in the thing described in the [prior art] reference, and that it would be so recognized by persons of ordinary skill." M.P.E.P. 2112 (citing *In re Robinson* 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999)). Thus, it was improper to suggest that Emilie *et al.* and Sato *et al.* rendered the claimed invention obvious "because the *specification* discloses that said elevated level of calcium is due to the production of IL-6." Final Office Action, pages 2-3 (emphasis added).

The Examiner provided no evidence that one of skill in the art at the time of filing would have recognized that ionized calcium is elevated in the blood of

cachexia animals/patients. Likewise, the Examiner provided no evidence suggesting that an anti-IL-6R antibody suppressed the ionized calcium elevation in cachexia animals/patients. The present specification teaches these findings for the first time. *See* specification, page 25, line 36 – page 26, line 3; page 26, line 35 – page 27, line 2 (describing experiments with colon 26-induced cachexia models and occ-1-induced cachexia models). In contrast, Emilie *et al.* and/or Sato *et al.* do not teach or even suggest anything relating to ionized calcium blood levels in cachexia patients.

Emilie et al. and/or Sato et al. do not teach or suggest all elements of the claimed invention

Emilie *et al.* do not discuss administration of an antibody raised against the IL-6 receptor. Moreover, although the Emilie reference teaches that administration of an anti-IL-6 antibody (i.e., against IL-6, not its receptor) affects fever and cachexia in patients with lymphomas associated with HIV infection, this reference does not teach or suggest that elevated blood levels of ionized calcium (i.e., hypercalcemia) accompanies cachexia. Similarly, this reference does not disclose or suggest that hypercalcemia should be controlled in cachexia patients, or that it can be controlled by administration of an anti-IL-6 receptor antibody. In fact, Emilie *et al.* fails to mention hypercalcemia at all, much less suggest any relation between hypercalcemia and IL-6 or its receptor.

Likewise, the Examiner provided no objective evidence that one of skill in the art understood that a cachexia patient necessarily suffers from hypercalcemia. As discussed above, the Examiner must provide evidence that "the missing descriptive matter is *necessarily* present in the thing described in the [prior art] reference, and *that it would be so recognized by persons of ordinary skill.*" *In re Robinson* 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999) (emphasis added); *see also* M.P.E.P. 2112. Without benefit of Applicants' specification, one skilled in

the art would not have recognized that an anti-IL-6 receptor antibody suppresses hypercalcemia in cachexia patients, or even that hypercalcemia accompanies cachexia.

Furthermore, even assuming (as is not the case here) that Emilie *et al.* disclosed a suppression of hypercalcemia in cachexia patients upon administration of the anti-IL-6 antibody, that disclosure would not have necessarily suggested the same result with an anti-IL-6 receptor antibody. To put it another way, the fact that an anti-IL-6 antibody blocked IL-6-induced cell signal transduction did not necessarily indicate that an anti-IL-6 receptor antibody would block the same signal transduction. Those skilled in the art knew that blood contained soluble IL-6 receptors, in addition to IL-6 receptors present on cell membranes. Skilled artisans therefore understood that anti-IL-6 receptor antibodies might bind to soluble IL-6 receptors, rather than cell surface IL-6 receptors. Consequently, a skilled artisan would not have recognized that an anti-IL-6 receptor antibody would *necessarily* block IL-6-induced signal transduction in cells.

In addition, skilled artisans also knew that blood contained a larger amount of IL-6 receptor compared to that of IL-6 (pg/ml level). Thus, skilled artisans would have believed that the amount of anti-IL-6 receptor antibody necessary to block IL-6-induced signal transduction would have been greater than that of the anti-IL-6 antibody. Thus, prior to the present invention, one of ordinary skill would not have necessarily expected to see similar results with an anti-IL-6 receptor antibody as with an anti-IL-6 antibody.

Like the Emilie reference, Sato *et al.* do not teach or suggest that hypercalcemia accompanies cachexia. The Sato reference simply indicates that an IL-6 receptor antibody inhibits growth of human multiple myeloma cell lines *in vitro*. Thus, this reference does not demonstrate any results *in vivo* or otherwise address concerns of those skilled in the art regarding the administration of antibodies against IL-6 receptor *in vivo* (e.g., that blood contains soluble IL-6 receptors, and

contains many more IL-6 receptors than IL-6 – *see* above discussion). Likewise, the Sato reference does not disclose or suggest that hypercalcemia should be controlled in cachexia patients, or that hypercalcemia can be controlled by administration of an anti-IL-6 receptor antibody. In fact, Sato *et al.* fails to mention cachexia or hypercalcemia at all, much less suggest any relation between hypercalcemia and IL-6 or its receptor.

Thus, Sato *et al.* fails to cure the deficiencies of Emilie *et al.* The claimed methods for using an anti-IL-6 receptor antibody to suppress elevated blood levels of ionized calcium in cachexia patients were unknown to those skilled in the art prior to Applicants' invention. Neither Emilie *et al.* or Sato *et al.*, alone or in combination, taught or suggested methods for suppressing hypercalcemia in cachexia patients by administering anti-IL-6 receptor antibodies. Neither reference mentioned hypercalcemia at all, or suggested any relation between hypercalcemia and IL-6 or its receptor.

The Examiner has provided no objective evidence that all claimed elements were *necessarily* present in the experiments described in Emilie *et al.* and Sato *et al.*, or that the claimed elements would have been recognized by persons of ordinary skill. Applicants' specification discloses for the first time that elevated levels of calcium correlates with cachexia (i.e., in a tumor-bearing control group, as compared to the non-tumor-bearing control group; *see* Figures 15 and 18 of the specification). Applicants' specification discloses for the first time that administration of antibodies against IL-6 receptors to patients can suppress the elevation of blood levels of ionized calcium accompanied by cachexia. The prior art cited by the Examiner did not teach, suggest or otherwise motivate those skilled in the art to practice Appellants' claimed methods with a reasonable expectation of success.

In summary, the Examiner has not established a *prima facie* showing of obviousness. Emilie *et al.* and/or Sato *et al.* did not, expressly or inherently, teach or suggest all elements of the claimed invention to those skilled in the art at the time of Applicants' filing. Accordingly, Applicants respectfully request that the Examiner withdraw the rejection under § 103(a).

CONCLUSION

In view of the foregoing remarks it is believed that the application is in condition for allowance. A favorable disposition of the application therefore is solicited. The examiner also is invited to contact the undersigned if there are any questions or if the examiner believes that further discussion will advance prosecution.

Respectfully submitted,

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June 19, 2003
Date

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Should additional fees be necessary in connection with the filing of this paper, or if a petition for extension of time is required for timely acceptance of same, the Commissioner is hereby authorized to charge Deposit Account No. 19-0741 for any such fees; and applicant(s) hereby petition for any needed extension of time.

APPENDIX I: Pending claims

15. A method of treating a patient suffering from an elevated blood level of ionized calcium accompanied by cachexia caused by interleukin-6 (IL-6) production comprising administering to said patient a therapeutically effective amount of an antibody to an IL-6 receptor in a pharmaceutically acceptable carrier to suppress elevation of blood level of ionized calcium and wherein the therapeutically effective amount blocks signal transduction by IL-6 and inhibits the binding of IL-6 to the IL-6 receptor.

24. The method according to claim 15, wherein said antibody is a monoclonal antibody.

25. The method according to claim 24, wherein said monoclonal antibody is the PM-1 antibody produced by hybridoma PM-1, accession number FERM BP-2998.

26. The method according to claim 24, wherein said monoclonal antibody is a chimeric antibody comprising the variable immunoglobulin heavy and light chains from a murine monoclonal antibody to an IL-6 receptor and the constant immunoglobulin heavy and light chains from a human monoclonal antibody.

27. The method according to claim 24, wherein said monoclonal antibody is a humanized murine monoclonal antibody to an IL-6 receptor.

28. The method according to claim 27, wherein said humanized murine monoclonal antibody to an IL-6 receptor is a humanized PM-1 antibody, wherein the PM-1 antibody prior to humanization is produced by hybridoma PM-1, accession number FERM BP-2998.